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SUPPLEMENT TO

THROMBOSIS RESEARCH

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THROMBOSIS RESEARCH

Founded by A.L. Copley

CONTENTS

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Supplement Issue

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THROMBOSIS RESEARCH

SUPPLEMENT ISSUE

The Results of CAPRIE, IST and CAST

Diederik W.J. Dippel
Department of Neurology, University Hospital Rotterdam, The Netherlands.

Abstract

The role of aspirin in the secondary prevention of ischaemic events is being challenged. CAPRIE, a blinded multicenter randomized trial of over 19000 patients followed for 1–3 years, assessed the effect of clopidogrel in the secondary prevention of major vascular events. Patients with a recent myocardial infarction, stroke or peripheral arterial disease were randomized to treatment with clopidogrel or aspirin. Clopidogrel was associated with a statistically significant, overall 8.7%, relative reduction in the risk of ischaemic events, but the direction and size of the effect was not homogeneous with respect to three predefined clinical subgroups. Clopidogrel may be slightly better in preventing major ischaemic events in high-risk patients, but the results of CAPRIE suggest that there is room for doubt. It remains to be seen whether treatment with clopidogrel is cost-effective compared with aspirin. However, aspirin, may still be of value in the early treatment of acute stroke. IST was a 20,000 patient, randomized, open-label study of aspirin plus heparin or neither in patients with acute ischaemic stroke that should be treated in 48 hours. There was a small but statistically nonsignificant reduction in mortality and disability at 6 months for patients allocated to early treatment with aspirin compared with those who were scheduled to avoid aspirin in the first 2 weeks after the stroke. Similar results were seen in CAST, a double-blind trial of aspirin vs. placebo in patients with suspected ischaemic stroke treated within 48 hours. A meta-analysis of the results of IST, CAST and MAST-I showed a statistically significant effect of early aspirin treatment. The role of aspirin in the treatment of acute stroke within 48 hours appears to be established.

Key Words: Aspirin; Clopidogrel; Secondary prevention; Ischaemia; Stroke

At the same time that the leading role of aspirin in the secondary prevention of ischaemic events is being challenged by other promising drugs that have been tested in large, randomized clinical trials, evidence has been brought forward that aspirin may also be valuable in the early treatment of acute stroke. This evidence will be discussed in this paper, but first the challenge of clopidogrel on aspirin's position as drug of first choice in secondary prevention will be more closely examined.

1. Secondary Prevention

We know that aspirin has a preventive effect on the occurrence of stroke, myocardial infarction, and vascular death, although the size of the effect is rather small. The overall odds reduction in all trials of patients with ischaemic vascular disease was 27% [1], but in a meta-analysis of all trials of aspirin alone (any dose) vs. placebo in patients with a recent transient ischaemic attack or non-disabling stroke, the relative odds reduction was only 16% (95% confidence interval: 5 to 26%) [2]. Finding more effective drugs for secondary prevention in patients at risk of vascular ischaemic events is therefore important.

CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events) [3] was a large, well-

Abbreviations: CAPRIE, Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events; CAST; Chinese Acute Stroke Trial; IST; International Stroke Trial; MAST-I; Multicentre Acute Stroke Trial—Italy.

Corresponding author: Diederik W.J. Dippel, Associate Professor in Neurology, University Hospital Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.

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Table 1. CAPRIE: Effects of clopidogrel by treatment group

Treatment group	N	First outcome events	Event rate per year (%)	Relative risk reduction (95% CI)
Stroke				
Aspirin	3198	461	7.71	7.3
Clopidogrel	3233	433	7.15	(−5.7–18.7)
MI				
Aspirin	3159	283	4.84	−3.7
Clopidogrel	3143	291	5.03	(−22.1–12.0)
PAD				
Aspirin	3229	277	4.86	23.8
Clopidogrel	3223	215	3.71	(8.9–36.2)
All patients				
Aspirin	9586	1021	5.83	8.7
Clopidogrel	9599	939	5.32	(0.3–16.5)

CI, confidence interval; MI, myocardial infarction; PAD, peripheral arterial disease.

designed and well-organized blinded, multicenter trial that aimed to assess the effect of the novel platelet-aggregation inhibitor clopidogrel in the secondary prevention of major vascular events. Clopidogrel is a thienopyridine derivative and is chemically related to ticlopidine [4,5]. It blocks platelet activation by irreversibly binding to the adenosine diphosphate (ADP) receptor and affects glycoprotein (GP) IIb/IIIa complex activation. In CAPRIE, more than 19,000 patients with either recent myocardial infarction, recent ischaemic stroke or symptomatic peripheral arterial disease were randomized for treatment with clopidogrel or aspirin. Patients were followed for 1–3 years.

In the intention-to-treat analysis, clopidogrel was associated with a statistically significant relative reduction in the risk of ischaemic events of 8.7% (95% CI: 0.3 to 16.5%). The absolute reduction in the annual rate of major ischaemic events was 0.5%. However, the direction and the size of the effect were not homogeneous in three predefined, prestratified clinical subgroups of patients (Table 1). In fact, in the myocardial infarction patients who were treated with clopidogrel, the risk of an outcome event was larger than in those treated with aspirin, although this was not statistically significant. An explanation for this heterogeneity is difficult to give, and it is certainly not caused by differences in baseline risk (see Table 1). It was argued that there was no compelling reason to assume heterogeneity in treatment effects across these strata, and that in the antiplatelet collaboration the odds reductions were markedly similar for the main subgroups of patients. In a post hoc analysis, all patients (including 2144 from the stroke or peripheral arterial disease subgroups) who had experienced myocardial infarction any time before randomization were included in a new subgroup. In this subgroup, the relative risk reduction was about 8%. Still, it is doubtful whether cardiologists would be happy and confident that clopidogrel is the drug of choice for their patients.

What does a relative risk reduction mean in real life? Calculations show that to prevent one major ischaemic event, assuming a 16% risk reduction and a baseline risk of 7% per year, 90–100 patients should be treated with aspirin during 1 year. For clopidogrel, with its additional (absolute) risk reduction of 0.5%, this number would be 70. The costs of a regimen of low-dose aspirin in the Netherlands is about $30 per patient-year. The costs of a patient-year of treatment with clopidogrel will undoubtedly be very much higher. It is open to question whether this treatment compares favorably with other common treatments in terms of cost-effectiveness.

2. Acute Stroke Treatment

Until now, we did not know whether aspirin could be safely and effectively administered to patients directly after they had experienced a stroke. The International Stroke Trial (IST) [6] was a large, randomized, open-label study of neither or both aspirin and subcutaneous heparin (low or medium dose) in patients with acute ischaemic stroke that should be

Table 2. Main absolute effects of aspirin in IST, CAST, and MAST-I

	IST	CAST	IST, CAST, MAST-I
Recurrent ischaemic stroke[a]	1.1 (0.5–1.7)	0.4 (0.2–0.7)	0.7 (0.3–1.1)
Haemorrhagic stroke	−0.1 (−0.3–0.1)	−0.2 (−0.5–0.1)	−0.2 (−0.4–0)
Death (from any cause)	0.4 (−0.4–1.2)	0.5 (0–0.8)	0.5 (0.1–0.9)
Death or non-fatal stroke	1.1 (0.1–2.1)	0.7 (0.4–1.0)	0.9 (0.3–1.5)
Dead or dependent[b]	1.3 (−0.1–2.7)	1.1 (−0.2–2.4)	1.3 (0.3–2.3)

[a] Recurrent ischaemic stroke (including stroke from unknown origin), haemorrhagic stroke, death and death or non-fatal stroke at end of treatment period (i.e., up to 4 weeks for CAST, 2 weeks for IST, at 10 days for MAST-I).

[b] At end of follow-up (i.e., at discharge for CAST, at 6 months for IST and MAST-I); 95% confidence intervals between brackets.

treated within 48 hours. In most patients, follow-up at 6 months was done blindly. Almost 20,000 patients were included in the study. Full follow-up was achieved in more than 99% of the patients. The results of this study indicated a small, almost statistically significant reduction in the main outcome event, (mortality and disability at 6 months) for patients allocated to early treatment with aspirin, compared to those who were to avoid aspirin during the first 2 weeks after the stroke. The absolute reduction in risk of death or disability was 1.3% (95% CI: −0.1–2.7%; p=0.06). At 14 days, there was already a significant reduction in recurrent ischaemic stroke, and in death or non-fatal stroke, both of 1.1%. This suggests that the benefit observed at 6 months was already achieved within the period of 2 weeks where trial aspirin was given. The positive and negative effects of subcutaneous heparin however, seemed to balance each other exactly.

The Chinese Acute Stroke Trial (CAST) was a double-blind trial of aspirin (150 mg) vs. placebo in patients with suspected acute ischaemic stroke, treated within 48 hours [7]. Its design was quite similar to the IST. Patients and investigators were blinded to the treatment allocation, a slightly lower aspirin dose was used for a longer period of 4 weeks, and follow-up was ended at discharge from hospital, but these are only minor differences. The trial was planned prospectively to be analyzed in parallel with the concurrent IST. However, the overall pattern of results of CAST is strikingly similar to IST; as is the size of the effect: A near significant decrease in patients who were dependent or dead at the end of follow-up was at least partly attributable to a significantly decreased number of recurrent ischaemic strokes, and a slight nonsignificant increase in haemorrhagic strokes. After combining the results of IST, CAST, and the much smaller Multicentre Acute Stroke Trial–Italy (MAST–I) [8] in a meta-analysis, the effect of early aspirin treatment became statistically significant (Table 2) [7].

3. Discussion

Although clopidogrel seems to be slightly better in preventing fatal and non-fatal heart attacks and strokes in patients at high risk of these events, there is room for doubt, as there is no direct proof of an effect in patients with recent myocardial infarction. Moreover, we do not know yet at what financial cost this benefit will be attained.

The days of aspirin as the drug of choice in secondary prevention are now hopefully numbered. Several other promising drugs are now being evaluated: For dipyridamole, that seemed to be more effective in combination with aspirin than either drug alone in the much debated and criticized ESPS-2 trial [9], more evidence will arise from the newly started European-Australian Stroke Prevention in Reversible Ischaemia Trial, that compares the effects of oral anticoagulant drugs (with international normalized ratios of 2–3), the combination of aspirin and dipyridamole, and aspirin alone in patients with transient ischaemic attack or nondisabling stroke [10].

Meanwhile, the role of aspirin in the treatment of acute stroke seems to be established. There is now (after two megatrials of acute stroke treatment) convincing evidence of a small effect, that indicates the prevention of approximately 10 patients less disabled or dead per 1000 treated, when aspirin is started immediately, instead of after 2–4 weeks. We not only have proof of an effect, but we also have a rationale for treating patients early with aspirin. Van Kooten et al. showed that during

Table 3. Number needed to treat to prevent one major ischaemic event

Drug	Indication	Treatment time	Number needed to treat
Aspirin	Secondary prevention	1 year	90
Aspirin	Acute stroke treatment	2 weeks	100
Clopidogrel	Secondary prevention	1 year	80

the first 48 hours after stroke there is substantial platelet activation, and this can be inhibited by aspirin [11,12]. Although the effect of aspirin seems small, one should be aware that it is of the same order of magnitude as the effect that can be expected of treating a patient with a transient ischaemic attack or nondisabling stroke during a whole year (Table 3).

In the author's opinion, neurologists and stroke physicians should consider prescribing aspirin to all patients with acute ischaemic stroke who come to their notice within 48 hours. They should not argue about exact aspirin dosages, but continue their contributions to randomized trials that test promising new drugs for secondary prevention and for acute stroke treatment.

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